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THE PATENT OFFICE
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Request for grant of a patent

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29 JUN 1999

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1.	Your reference	44.70360/000
2.	Patent application number *(The Patent Office will fill in this part)*	9915184.7
3.	Full name, address and postcode of the or of each applicant *(underline all surnames)*	A-Viral AS Karihaugveien 102 N-1006 Oslo Norway
	Patents ADP number *(if you know it)*	75759390001 MB
	If the applicant is a corporate body, give country/state of incorporation	Norway
4.	Title of the invention	Compounds
5.	Name of your agent *(if you have one)*	Frank B. Dehn & Co.
	"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	179 Queen Victoria Street London EC4V 4EL
	Patents ADP number *(if you know it)*	166001

6.	If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number	Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7.	If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application	Date of filing *(day / month / year)*

8.	Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:* *a) any applicant named in part 3 is not an inventor, or* *b) there is an inventor who is not named as an applicant, or* *c) any named applicant is a corporate body.* *See note (d))*	Yes

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Continuation sheets of this form	0
Description	13
Claim(s)	3
Abstract	-
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10. If you are also filing any of the following, state how many against each item.

Priority documents	-
Translations of priority documents	-
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	-
Request for preliminary examination and search *(Patents Form 9/77)*	-
Request for substantive examination *(Patents Form 10/77)*	-
Any other documents *(please specify)*	-

11. I/We request the grant of a patent on the basis of this application.

Signature Date 29th June 1999
Frank B Dehn & Co

12. Name and daytime telephone number of person to contact in the United Kingdom

Julian Cockbain
0171 206 0600

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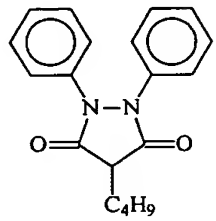
70360/000.605

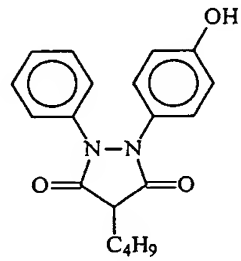
Compounds

The present invention relates to certain pyrazolidinols and their sulphur (i.e. thio/thiol) analogs and pharmaceutical compositions thereof for use in antiviral, e.g. anti-HIV therapy and as anti-inflammatories.

Phenbutazone and oxyphenbutazone are 1,2-bis aromatic-3,5-pyrazolidinediones which have been used as non-steroidal anti-inflammatory drugs (NSAIDs)



Phenbutazone (PB)



Oxyphenbutazone (OPB)

Other 3,5-pyrazolidinediones have likewise been proposed for use as NSAIDs (see for example US-A-3968219 (Rahtz)) and the hydroxy-protected enol forms have been proposed as pro-drug forms of phenbutazone and oxyphenbutazone (see US-A-4117232 (Bodor), US-A-3957803 (Bodor), US-A-4169147 (Bodor), US-A-4036845 (Bodor) and US-A-4139709 (Bodor)).

In US-A-4956377 (Miesch) it was proposed that this class of NSAIDs had utility as an antiviral agent, in particular for the treatment of HIV.

We have now surprisingly found that where the 4-carbon of the N_2C_3 ring carries an optionally protected

hydroxy or thiol group, the compounds have very significantly enhanced antiviral, in particular anti-HIV, efficacy.

Thus viewed from one aspect the invention provides the use of an optionally hydroxy-protected 4-hydroxy or hydroperoxy-3,5-dioxo-pyrazolidine or an equivalent wherein a pyrazolidine ring attached oxygen is replaced by a sulphur, or a physiologically acceptable salt thereof, for the manufacture of a medicament for use in therapy or prophylaxis.

Where a particular 4-hydroxy or hydroperoxy-3,5-dioxo-pyrazolidine may exist in more than one stereoisomeric form, it may be used in single isomer form or as an isomer mixture, e.g. a racemic mixture.

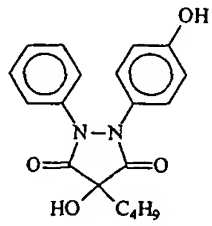
Viewed from a further aspect, the invention provides an optionally hydroxy-protected 4-hydroxy or hydroperoxy-3,5-dioxo-pyrazolidine or an equivalent wherein a pyrazolidine ring attached oxygen is replaced by a sulphur, or a physiologically acceptable salt thereof.

Viewed from a still further aspect the invention provides a method of treatment of the human or non-human (e.g. mammalian, reptilian or avian) body to combat an inflammatory or viral disease, preferably an immuno-deficiency viral disease, in particular HIV, which method comprises administering to said body an optionally hydroxy-protected 4-hydroxy or hydroperoxy-3,5-dioxo-pyrazolidine or an equivalent wherein a pyrazolidine ring attached oxygen is replaced by a sulphur, or a physiologically acceptable salt thereof.

Viewed from a still further aspect, the invention provides a pharmaceutical composition comprising an optionally hydroxy-protected 4-hydroxy or hydroperoxy-3,5-dioxo-pyrazolidine or an equivalent wherein a pyrazolidine ring attached oxygen is replaced by a sulphur, or a physiologically acceptable salt thereof, together with at least one pharmaceutically acceptable

carrier or excipient.

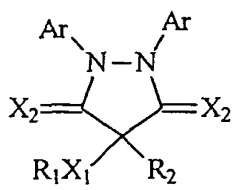
The applicants have found that oxyphenbutazone, as commercially available, contains minute quantities of certain impurities, presumably as a result of undesired oxidative breakdown. One of these, present at about 0.4% wt, is 4-butyl-4-hydroxy-2(p-hydroxyphenyl)-1-phenyl-3,5-pyrazolidinedione (hereinafter "4-OH-OPB"), i.e.



4 OH-OPB

4-OH-OPB is of course a compound according to the invention and thus it should be understood that references to the 4-hydroxy compounds of the invention, their use and compositions thereof should not be taken to include references to such compounds when in intimate admixture with overwhelmingly larger quantities of a 3,5-pyrazolidinedione which carries no optionally protected 4-hydroxy or 4-thiol group. By overwhelmingly larger is meant a relative weight ratio of at least 98:2. In general, the compounds of the invention should not desirably be used in intimate admixture with larger quantities (i.e. a relative weight ratio of more than 50:50) of such compounds carrying no O or S attached group at the 4-position, and more desirably they should not be used with such compounds present in greater than 10:90 weight ratio.

The compounds of the invention, hereinafter referred to as pyrazolidinols for convenience, will preferably be of formula I



(I)

(where each X_2, which may be the same or different is O or S,
X_1 is O, OO or S, preferably O or S, most preferably O,
R_1 is hydrogen or a hydroxyl or thiol protecting group (e.g. an acyl group, preferably containing up to 6 carbons, e.g. an acyl group such as an alkylcarbonyl group, for example acetyl),
R_2 is hydrogen or more preferably a carbon attached organic group containing up to 10 carbons, e.g. an alkyl, alkenyl, alkynyl, alkaryl, aralkyl or aralkenyl group, and
each Ar, which may be the same or different, is a homo or heterocyclic aromatic group) or a salt thereof.

In the compounds of the invention 0, 1 or 2 of the X_1 and X_2 groups may be S. It is thought that it is especially preferred that one thio X_2 group be present.

In the compounds of the invention, the R_2 group is preferably other than hydrogen and may for example be straight chain, branched, cyclic or cyclic-attached-to-straight chain. Preferably it is an alkyl or alkenyl group, especially a C_{1-6} alkyl or alkenyl group, e.g. n-propyl, n-butyl, n-pentyl or 1-methyl-but-2-en-4-yl.

Where R_1 in the compounds of the invention is other than hydrogen it is preferably a metabolically labile hydroxy- or thiol-protecting group which yields a physiologically tolerable R_1OH metabolite. Acyl groups are preferred in this regard.

In the compounds of formula I, where each X_2 is oxygen and one Ar is phenyl, the other Ar is preferably other than phenyl or parahydroxyphenyl.

A wide range of hydroxy- and thiol-protecting groups however is known from the literature (see McOmie, "Protective groups in organic chemistry", Plenum, 1973 and Greene, "Protective groups in organic synthesis", Wiley Interscience, NY, 1981) and many compounds of formula I in which R_1 is a protecting group may be useful as intermediates in the production of compounds of

formula I in which R_1 is hydrogen.

The Ar groups in the compounds of formula I are preferably 5 to 7 membered aromatic rings, optionally carrying a fused aromatic ring and optionally substituted on ring atoms, for example by C_{1-6} alkyl groups but especially by electron withdrawing substituents, e.g. hydroxy, thiol, phenyl, C_{1-6} alkoxy, cyano, halo (e.g. Cl, F, Br or I), protected hydroxy, or protected thiol. Ring heteroatoms will generally be selected from O, N and S, preferably with a single ring heteroatom in any aromatic Ar heterocycle. Ar is preferably phenyl optionally substituted, especially in the para-position by $-X_1-R_1$ or Cl (where $-X_1-R_1$ is as defined above). Especially preferably one Ar is phenyl and the other is p-hydroxy-phenyl.

Where the substitution of the pyrazolidinols of the invention is such that they may form addition salts with acids or bases, the addition salts which have physiologically tolerable counterions are of course preferred, e.g. sodium, organic amine, halides, phosphates, hydrogen carbonates, etc.

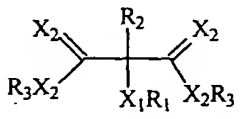
The pyrazolidinols of the invention may particularly advantageously be used in combination therapy with other antiviral, especially anti-HIV, agents, in particular reverse transcriptase inhibitors and/or protease inhibitors, e.g. zidovudine, didanovine, zalcitabine, stavudine, lamivudine, nevirapine, delavirdine, indinavir, ritonavir and nelfinavir. Such combination therapy forms a further aspect of the present invention.

The pyrazolidinols of the invention may be prepared by oxidation of a corresponding compound where R_1X_1 is replaced by hydrogen; by reaction of a corresponding compound where R_1X_1 is HX_1 with a hydroxy or thiol protecting agent to introduce a non-hydrogen R_1 group; or by condensation of a hydrazine derivative with an optionally protected 2-hydroxy-propane dioic acid ester

(or a sulphur analog), e.g. by condensation of a compound of formula II

$$Ar - HN - NH - Ar \qquad (II)$$

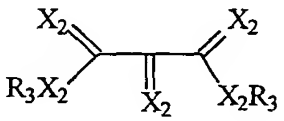
with a compound of formula III



(III)

where R_1, R_2, X_1, X_2 and Ar are as hereinbefore defined and X_2R_3 is a leaving group, for example where R_3 is an alkyl group, e.g. a C_{1-6} alkyl group.

Alternatively, a compound of formula II may be condensed with a compound of formula IV



(IV)

(where X_2 and R_3 are as defined above) and then reacted with an alkylating agent, e.g. $(R_2)_2Zn$ to produce a compound of formula I in which X_1R_1 is OH or SH.

For administration, the pyrazolidinols of the invention may be formulated in any convenient form, e.g. tablets, coated tablets (e.g. delayed release tablets), capsules, solutions, suspensions, dispersions, syrups, powders, sprays, suppositories, transdermal patches, gels, emulsions and creams. Administration may be via any convenient route, e.g. oral, rectal, transdermal, nasal, subcutaneous, intravenous, intramuscular, etc. Oral administration, e.g. of tablets or capsules is preferred. The pyrazolidinols may be formulated together with conventional pharmaceutical carriers, diluents or excipients, e.g. aqueous carriers (for

example water for injections), binders, fillers, stabilizers, osmolality adjusting agents, effervescing agents, pH modifiers, viscosity modifiers, sweeteners, lubricants, emulsifiers, flavours, coating agents (e.g. gastric juice resistant coatings), etc.

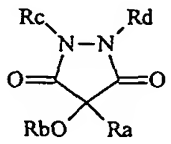
The dosage of the pyrazolidinols given according to the invention will depend on the size and species of the subject being treated but will generally be in the range of 0.05 to 2000 mg/day, more particularly 0.5 to 1000 mg/day, especially 1 to 100 mg/day, preferably with administration being effected once, twice, three times or four times daily.

For regular, e.g. continuous daily treatment according to the invention, the daily dosage of the pyrazolidinol will preferably be in the range 5nmol to 2 μmol/kg bodyweight, more preferably 100 nmol to 1.5 μmol/kg, especially 500 nmol to 1 μmol/kg. However, in a particularly preferred embodiment of the invention, a pyrazolidinol according to the invention is administered at a dose sufficient to suppress T-lymphocyte (CD4 cell) growth (e.g. a daily dose of 0.1 to 10 μmol/kg) for a period of 1 to 14 days, preferably 2 to 7 days at intervals of at least 3 months, preferably at least 9 months, e.g. 10 to 18 months. In this way the patient's immune system may be "refreshed" by removal of the preponderance of T-lymphocytes directed to HIV antigens. Such a treatment indeed is novel and forms a further aspect of the invention. Viewed from this aspect the invention provides a method of combatting HIV infection which comprises administering to an HIV-infected patient a T-lymphocyte growth suppressing agent, e.g. a pyrazolidinol, in an amount sufficient to suppress T-lymphocyte growth in said patient for a period sufficient to reduce the T-lymphocyte concentration in lymph nodes in said patient by at least 25%, more preferably at least 50%, said administration being repeated at intervals of at least 3 months, preferably

at least 9 months.

Besides HIV, the pyrazolidinols of the invention may be used to combat other viral infections, especially retroviral infections but also infections by togaviridea, reoviridea, picornaviridea, hantaviridea, orthomyxoviridea, paramyxoviridea, mononegaviralis, viral hepatitis, haemorrhagic fevers, flaviviridea, viral encephalitis, coronaviridea, calciviridea, adenoviridea, papovaviridea, arboviridea, pox virus, rhabdoviridea, herpes virus and arenaviridea. The pyrazolidinols of the invention may in particular be used to combat viral infections of CD4 cells, e.g. HIV-1, HIV-2, HTLV-I, HTLV-II and herpes viruses, for example to combat AIDS, T-cell tumours (e.g. Sezary Syndrome, mycosis fungoides, and T-cell lymphoma), tropic spastic paraparesis, and Karposi's sarcoma. Moreover despite not being of the accepted formula for NSAIDs (which would require an acid proton in place of R_1X_1 at the 4-position), they may be used as anti-inflammatory drugs. All these uses form aspects of the invention.

Various 4-hydroxy-3,5-dioxo-pyrazolidines are known in the literature (although not for medical purposes such as HIV therapy). These are compounds of formula V



(V)

where R_a to R_d are as set out in Table 1 below:

Table 1

R_a	R_b	R_c	R_d
H	H	H	C_6H_5
H	H	C_6H_5	C_6H_5
CH_3	H	H	C_6H_5
CH_3	H	H	$-CH_2-C_6H_5$
CH_3	H	H	$p-CH_3O-C_6H_4$
CH_3	H	H	$p-Cl-C_6H_4$
C_2H_5	H	H	C_6H_5
C_2H_5	H	C_6H_5	C_6H_5
C_2H_5	H	H	N-methyl-piperidin-4-yl
iC_3H_7	H	H	C_6H_5
nC_3H_7	H	H	C_6H_5
nC_3H_7	H	C_6H_5	C_6H_5
nC_3H_7	H	H	5-phenyl-triazol-1-yl
C_4H_9	H	H	C_6H_5
C_4H_9	H	C_6H_5	C_6H_5
C_4H_9	H	C_6H_5	$p-OH-C_6H_4$
C_4H_9	OH	C_6H_5	C_6H_5
C_4H_9	OH	C_6H_5	$p-OH-C_6H_4$
C_4H_9	H	H	N-methyl-piperidin-4-yl
C_5H_{11}	H	H	C_6H_5
C_5H_{11}	H	C_6H_5	C_6H_5
C_5H_{11}	H	H	5-phenyl-triazol-1-yl
Cyclohexyl	H	H	C_6H_5
Phenyl	H	H	C_6H_5
Phenyl	H	C_6H_5	C_6H_5
Benzyl	H	H	C_6H_5
Benzyl	H	C_6H_5	C_6H_5
$CH_3CO(CH_2)_2$	H	C_6H_5	C_6H_5
$(CH_3)_2C=CH-$	H	C_6H_5	C_6H_5
$(CH_2)_2C=CHCH_2$	H	C_6H_5	C_6H_5
$C_6H_5SCH_2CH_2$	H	C_6H_5	C_6H_5
Pyrrolidin-1-yl	H	C_6H_5	C_6H_5
Piperidin-1-yl	H	C_6H_5	C_6H_5
Morpholin-4-yl	H	C_6H_5	C_6H_5

Such compounds are thus not claimed per se herein; however their use and pharmaceutical compositions containing them do form part of the scope of the invention.

The invention will now be illustrated further by the following non-limiting Examples:

EXAMPLE 1

Preparation of 4-butyl-4-hydroxy-2(p-hydroxyphenyl)-1-phenyl-3,5-pyrazolidinedione (4OH-OPB-AV1001)

Oxyphenbutazone.H_2O (1 mmol), 30% H_2O_2 (0.7 mL), 1N NaOH (0.1 mL) and methanol (3.5 mL) are allowed to stand for 13 hours at ambient temperature. The mixture is then poured into 5% HCl (20 mL) and extracted with ethyl acetate (2 x 20 mL). The ethyl acetate phase is separated, dried over sodium carbonate and the solvent is removed under reduced pressure without heating. The residue is subjected to flash chromatography (silica/ ethyl acetate). The title product is recrystallized from ethyl acetate.

EXAMPLE 2

Antiviral activity of 4OH-OPB

4OH-OPB was added to cultures of growing MT4 cells (a human CD4 cell line). HIV-1, stored in the culture medium at -75°C was thawed and added in an amount which infected about 1 in 7 cells in each culture. The virus was absorbed to the cells for 2.3 hours at ambient temperature whereafter the cultures were centrifuged at 1200 rpm, the medium was removed, the cells were suspended in fresh growth medium and 4OH-OPB was added to concentrations of 1, 10 and 100 μM (diluted in medium from a stock solution of 20 mM in DMSO). After 72 hours

the HIV antigen concentration was determined using Abbott's test. By way of comparison phenbutazone (PB) was tested analogously. The results are shown in Figure 1 and demonstrate inhibition of virus production by 4OH-OPB at concentrations above the lowest tested.

EXAMPLE 3

Preparation of capsules for oral use

4-OH OPB (Example 1)	50 mg
Amylum maydis	q.s.

The powder is mixed and filled into hard gelatin capsules (Capsugel size 00).

EXAMPLE 4

Preparation of tablets

	Gram
4-OH OPB (Example 1)	200
Lactose	85
Polyvinylpyrrolidone	5
Starch	42
Talcum powder	15
Magnesium stearate	3

4-OH OPB and lactose are screened through a 0.15 mm sieve and mixed together with an aqueous solution of polyvinyl-pyrrolidone. The mass is granulated, and the dried (40°C) granulate is mixed with starch, talcum powder and magnesium stearate. The granulate is compressed into tablets. The tablet diameter is 11 mm, the tablet weight is 350 mg and each tablet contains 200 mg 4-OH OPB.

EXAMPLE 5

Preparation of a suspension for rectal administration

Methyl p-hydroxybenzoate (70 mg) and propyl-p-hydroxybenzoate (15 mg) are dissolved in water (100 ml) at 90°C. After cooling to 30°C, methyl cellulose (2g) is added and the mixture is agitated for 3 hours. 1 gram 4-OH OPB (Example 1) is screened through a 0.15 mm sieve, and dispersed in the solution under vigorous stirring. The suspension is filled in a 100 ml tube. The suspension contains 10 mg 4-OH OPB/ml.

EXAMPLE 6

Preparation of oral suspension

	Gram
4OH OPB (Example 1)	10
Carboxymethyl cellulose	1.5
Sorbitol	200
Sodium benzoate	1.0
Orange essence	0.3
Apricot essence	0.7
Ethanol	50
Water	236.5

Carboxymethyl cellulose, sorbitol and sodium benzoate are dissolved in water with stirring for 2 hours. A solution of the essences in ethanol is added. 4-OH OPB is screened through a 0.15 mm sieve and dispersed in the solution under vigorous stirring. The suspension (10 gram) is filled in a 20 ml tube. Each tube contains 200 mg 4-OH OPB.

EXAMPLE 7

Mouse toxicity

20g mice were given single doses of 4OH-OPB (20 mM in DMSO) intraperitoneally. Doses of 1 to 100 μM (in ECF), corresponding to 0.29 to 29 μM/kg bodyweight, produced no toxic effect.

Claims

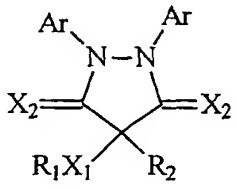
1. The use of an optionally hydroxy-protected 4-hydroxy or hydroperoxy-3,5-dioxo-pyrazolidine or an equivalent wherein a pyrazolidine ring attached oxygen is replaced by a sulphur, or a physiologically acceptable salt thereof, for the manufacture of a medicament for use in therapy or prophylaxis.

2. An optionally hydroxy-protected 4-hydroxy or hydroperoxy-3,5-dioxo-pyrazolidine or an equivalent wherein a pyrazolidine ring attached oxygen is replaced by a sulphur, or a physiologically acceptable salt thereof.

3. A method of treatment of the human or non-human body to combat an inflammatory or viral disease, which method comprises administering to said body an optionally hydroxy-protected 4-hydroxy or hydroperoxy-3,5-dioxo-pyrazolidine or an equivalent wherein a pyrazolidine ring attached oxygen is replaced by a sulphur, or a physiologically acceptable salt thereof.

4. A pharmaceutical composition comprising an optionally hydroxy-protected 4-hydroxy or hydroperoxy-3,5-dioxo-pyrazolidine or an equivalent wherein a pyrazolidine ring attached oxygen is replaced by a sulphur, or a physiologically acceptable salt thereof, together with at least one pharmaceutically acceptable carrier or excipient.

5. A compound of formula I



(I)

(where each X_2, which may be the same or different is O or S,
X_1 is O, OO or S,
R_1 is hydrogen or a hydroxyl or thiol protecting group,
R_2 is hydrogen or a carbon attached organic group containing up to 10 carbons, and
each Ar, which may be the same or different, is a homo or heterocyclic aromatic group) or a salt thereof.

6. A compound as claimed in claim 5 wherein each X_2 is oxygen, R_1X_1 is HO or $CH_3CO.O$, each Ar, which may be the same or different is optionally halo or hydroxy substituted phenyl, and R_2 is C_{1-6} alkyl or alkenyl, or a salt thereof.

7. 4-Butyl-4-hydroxy-2(p-hydroxyphenyl)-1-phenyl-3,5-pyrazolidinedione for use as a medicament.

8. A method of combatting HIV infection which comprises administering to an HIV-infected patient a T-lymphocyte growth suppressing agent, e.g. a pyrazolidinol, in an amount sufficient to suppress T-lymphocyte growth in said patient for a period sufficient to reduce the T-lymphocyte concentration in lymph nodes in said patient by at least 25% said administration being repeated at intervals of at least 3 months, preferably at least 9 months.

9. A method as claimed in claim 3 or claim 8 wherein a 4-hydroxy or hydroperoxy-3,5-dioxo-pyrazolidine or an equivalent wherein a pyrazolidine ring attached oxygen is replaced by a sulphur, or a physiologically acceptable salt thereof is administered in a daily dose of 0.1 to 10 μmol/kg bodyweight.

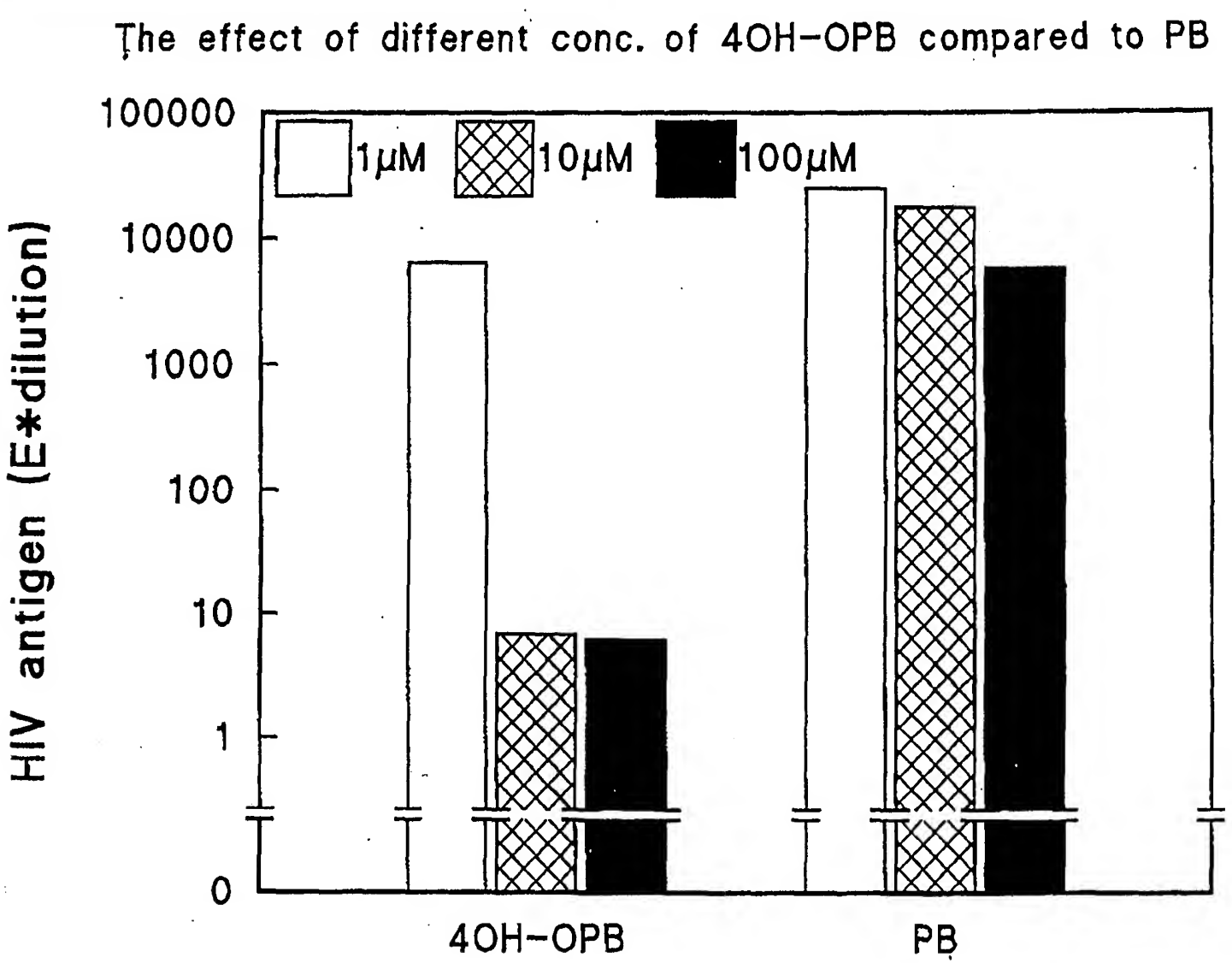
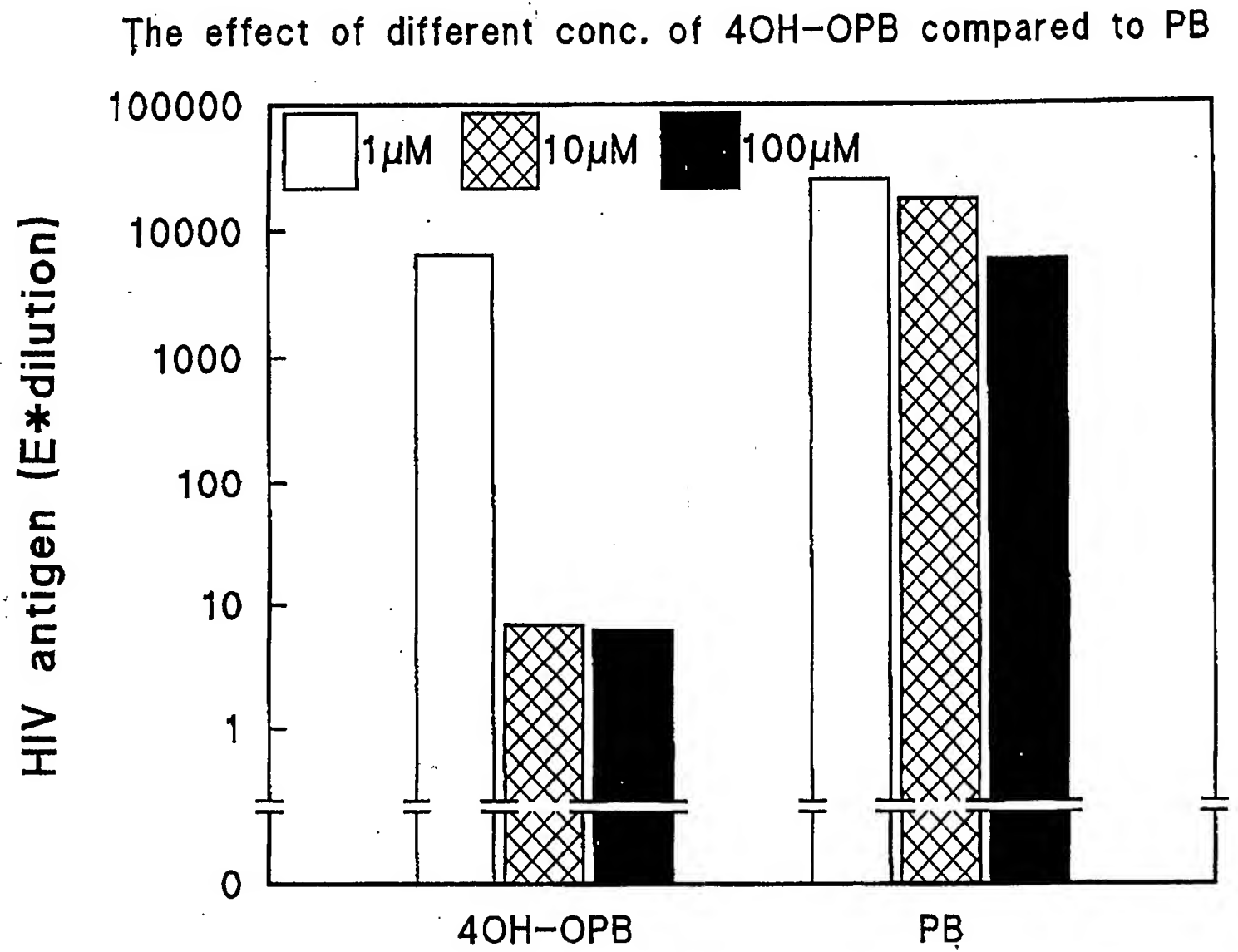

The effect of different conc. of 4OH-OPB compared to PB
HIV antigen (E*dilution)
100000
10000
1000
100
10
1
0
1μM
10μM
100μM
4OH-OPB
PB

FIGURE 1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PB

FIGURE 1

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Frank B. Dehn & Co.